THE MIXED TUMORS OF THE SALIVARY GLANDS.

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(*A Study from the Department of Pathology of Columbia University.*)

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SUMMARY OF THE CLINICAL COURSE AND GENERAL MORPHOLOGY OF THE TUMORS.

BEFORE summarizing the details of the results of the study of the cases just given, it may be well to note the relative frequency of occurrence of tumors in the salivary glands. Böhme, in a collection of a large number of tumors from this region, found that they occur in the parotid ten times more frequently than in the submaxillary, while the sublingual gland is the site of tumor formation only in 1 per cent. of the whole number examined. Küttner also gives the proportion as eleven to one. This proportion is not to be observed in my own series, for, taking those in which the source of the tumor is definitely recorded, the parotid growths number twenty-six, while the submaxillary number thirteen, or exactly half as many. That this is probably due to the fact that in preserving these tumors the rarer submaxillary growths were more often saved than the more abundant parotid growths is evident from the Pathological Records of St. Luke's Hospital, where the parotid growths operated upon are five times as numerous as the submaxillary. Of the fifty-nine tumors recorded in this paper only four are from the lip, four from the pharynx or palate, two from the neck, and one from the cheek. Even this cheek tumor was in contact with Steno's duct, and should probably be considered as connected genetically with the parotid.

If we consider the tumors from the point of view of the frequency of the mixed growths as compared to the other neoplasms of the salivary glands, we find that out of the fifty-nine cases one may possibly be considered as an adenoma and two as sarcomata, a third is a fragment of embryonic connective tissue, fat, and blood-vessels, the remainder may be considered as belonging to the mixed tumors or the so-called endotheliomata. The author has in his possession three carcinomata and one pure adenoma, while a pure myxoma, a rhabdomyoma, and a round-cell sarcoma are in the collection of the Pathological Department. Evidently the mixed tumors form a large proportion of the tumors arising in the salivary glands. Cases reported by other observers show the same proportion. Kaufmann in fifteen cases of salivary gland tumors saw one angiosarcoma; Nasse in thirty-six cases saw two carcinomata and two sarcomata; Volkmann in thirty-three cases saw one carcinoma, one myxoma which he is inclined to regard as of endothelial origin, and one fibrosarcoma. Landsteiner, who has already been quoted, saw only two purely epithelial tumors out of twenty-seven examined, the remainder being of the complex variety.

Volkmann also quotes Marchand as saying the greater proportion of the salivary tumors which the latter had seen were to be classed under the general group of endotheliomata, and that purely epithelial growths were of very great rarity. The tumors described by the French observers as adenomata or epitheliomata are usually of the complex type, and very few are either pure sarcomata or carcinomata.

Küttner in ninety-seven submaxillary tumors which he was able to collect from the literature found sixty-four endotheliomata, six sarcomata, three doubtful cases of adenoma, five carcinomata, and nineteen cases in which the description was so imperfect that no determination of the nature of the growth could be made. It is evident, therefore, that the mixed tumors form a very large proportion of the tumors of the salivary glands. As regards the pharynx and lips, it is a matter of common experience that the mixed tumors are exceedingly rare in these situations, and that the purely epithelial tumors are exceedingly frequent.

General Morphology.—The mixed tumors of the salivary glands are found, as a rule, to be encapsulated, lobular growths, with harder and softer areas, the denser portions being due, as a rule, to the presence of cartilage or firm connective tissue. They can be divided macroscopically into three great rough groups with characteristic morphology, and to a certain extent with a definite clinical course.

First. Very fibrous tumors with very little cellular structure and with but little mucous degeneration and no cartilage.

Second. Very hard tumors containing large masses of cartilage and but little connective tissue or cellular parenchyma.

Third. Soft, very cellular growths with transparent trabeculæ of mucous tissue surrounding areas which are opaque and yellow, which on microscopical examination will be found to be dense cellular areas, the color being occasionally, though not always, due to fatty degeneration or necrosis of the cells.

The first and second forms are likely to be benign in their clinical course, while the third form is likely to recur locally or to run an exceedingly malignant course.

A few of the parotid tumors examined and one from the pharynx belong to the first group; about one-fourth of the growths contain more or less cartilage and fall into the second; while the majority of the mixed tumors belong to the third. It must be remembered, however, that a great amount of variation is present in different parts of the same tumor, and while one portion may be cellular the other may be composed largely of cartilage.

The cellular tumors without cartilage, of the third class, have much the same consistency as an inflamed lymph node. The cut section of one of these tumors may show either a large amount of clear hyaline cartilage with a moderate amount of yellowish cellular substance lying between the pale blue translucent nodules of the cartilage, or the whole growth may be cellular and of a pale yellow or grayish hue, or, finally, the cartilage may be scattered throughout the tumor in the form of small nodules. Some of the tumors resemble very closely soft fibromata, especially if much mucous degeneration is present. If the surface of the more cellular growths is scraped with a knife, a milky fluid can be obtained which is due to the removal of the alveolar cells by the mechanical action of the knife.

The development of these tumors may take place before birth, in which case they are often associated with other congenital defects of the facial region. (Case L.) As a rule, however, the actual development of these growths becomes noticeable most frequently during the second decade of life.

Time of Occurrence.—In my own series the age at the time of the operation was as follows: one tumor under one year, seven between the ages of twenty and thirty, ten between thirty and forty, ten between forty and fifty, ten between fifty and sixty, and four over sixty. If the cases are subdivided according to the decade in which the tumor appeared, the age periods are somewhat different. Four tumors appeared in the first decade, one in the second, thirteen in the third, eight in the fourth, nine in the fifth, four in the sixth, while three still remain in the seventh.

The average age in these cases is then a little higher than that found by Kaufmann and Küttner, according to whom the majority of growths appeared in the second decade. The number of tumors from other regions of the face is too small to furnish useful statistics.

The average duration of these tumors until they cause the patient to seek surgical aid is in my series eight years and nine months, thus varying only slightly from the time given by other observers, eight years. A long clinical course is not uncommon; thus, Case VI gave a history of the presence of a tumor for twenty years, Case IV for fifty-three years. The social status of the patient may also determine a variation in the time which a tumor is allowed to remain, for among the working-classes these tumors often have a longer history than among the wealthy.

Relations of Tumors to Surrounding Structures.—The anatomical position and the relations of these tumors to the surrounding structures are often characteristic of growths of this type. They are seen in the pharynx attached to the bony structures of the hard palate, often indenting the substance of the bone, but not involving the bone substance. There is usually a thick fibrous capsule which separates the tumor from the periosteum, or the capsule of the tumor may be formed by the periosteum. They also occur on the inner surface of the cheeks, generally near the openings of Steno's duct, and in the substance of the lip, most often near the median line. They also occur in the cervical region in the upper triangle of the neck and in front of the sternocleidomastoid muscle. The most frequent situation, however, is near or in the substance of the parotid and submaxillary glands. Their relations in this case are most variable. The tumors may not be in any way connected with the gland but merely lie near it; they may be attached to the gland by a pedicle or be adherent to a small accessory gland; they may indent the surface of the gland, being separated from the acini by a fibrous-tissue capsule, or, finally, the tumors may be multiple and dot the substance of the gland itself.

Usually in large tumors the remains of the glandular tissue are stretched out over the surface of the tumor and undergo pressure atrophy, but are separated from the tumor substance by a capsule. In the pharynx, the lips, and the cheeks the tumors usually lie just below the surface of the mucous membrane; but the parotid, submaxillary, and cervical new growths are below the deep fascia. They are, however, unless of a large size, easily movable in the tissues. The larger tumors are fixed, not so much by invasion of the structures surrounding them as by the tight stretching of the fascia which they cause during their growth. In those cases in which the tumor becomes malignant, the immobility is due, of course, to the invasion of the surrounding tissues.

The skin is freely movable over the benign growths. The ear may be distorted or pressed entirely backward by a large tumor in the parotid region, especially if the growth has extensions behind the angle of the jaw, and is therefore unable to expand anteriorly.

Clinical Course.—Considering the mixed tumors from the face and neck as a group, we may say that an average of the cases in the literature shows that some 25 per cent. undergo changes which express themselves in a clinically malignant course, while about 30 per cent. recur after operative removal, though some of these recurrences may be stayed by a second and more complete removal. The records of my own series are somewhat different. Out of thirty-seven cases in which notes of the patient's condition after operation have been recorded, seventeen, or 45 per cent., recurred locally. In four of the cases either internal metastases were soon apparent or the local condition was so serious that the patients either died of operative shock, as in two cases, or became inoperable from the invasion of the bone and deep tissues of the neck. Of the remaining thirteen cases one is still alive after many operations, but will probably soon succumb to the growth, which is now beyond removal. In twelve cases, then, or nearly 33 per cent., there were local recurrences which were checked by operation, so that a second removal should always be attempted if the anatomical conditions permit of a complete removal of the new growth.

The malignancy of these growths can be judged to a certain extent by their slowness of growth and their physical characters. The hard fibrous and cartilaginous tumors are apt to be benign, while the soft cellular types are likely to prove malignant. But frequently a tumor which has remained for a long time quiescent will begin a most rapid growth (Case XXXVII), and in a few months increase in size more than during its entire previous existence. This sudden and rapid growth is accompanied by the clinical and microscopical evidences of malignancy, and the tumor spreads through the surrounding tissues, involves the skin and the salivary glands, and may form metastases, changes which are illustrated by Cases XXV, XXVIII, and XXXVI. Twenty cases out of thirty-seven, or 55 per cent., were permanently cured by operation.

No sufficient explanation has been adduced for the sudden change which takes place in the benign growths and causes them to become malignant. Kaufmann regards the constant traumatic irritation of the tumor by the muscles of mastication as a possible inciting agent.

It is quite probable that the dense fibrous capsule which surrounds these tumors contributes to their prolonged benign character by preventing the tumor cells from easily spreading through the tissue; for when this capsule is removed by operation on a quiescent tumor and small portions of the tumor cells are left behind in the scar, a rapid recurrence is the rule, and the new growth may reach a bulk in a few weeks greater than that of the original tumor, which may have taken years to develop. The increased vascularity of the tissues may have something to do with this rapidity of growth, for the comparative absence of blood-vessels in the primary mixed tumors is noteworthy. This poor blood supply in the original growths and the lack of close relationship between the cells of the tumors and the vessels may also be contributive to the comparative innocence of the mixed tumors, while in the sarcomata, with their very abundant blood supply and close relationship between cells and vessels, extreme malignancy is the rule. There is still a third element which must be considered as a possible factor in the development of malignancy in these growths, and that is the abundant embryonal connective tissue which is found in many of them. In two of the writer's cases of very malignant growths, the metastasis was purely sarcomatous; there was no alveolar arrangement of the cells and none of the other elements of the original tumor were present. It seems likely that the embryonal connective tissue of the original growth underwent a change which expressed itself in the formation of a rapidly growing sarcomatous tissue, and that the other elements of the tumor took no part in the process. The cartilage of the original tumor does not, as a rule, appear in the recurrences, and the amount of elastic tissue is in general much less than in the primary growth. In those cases in which a recurrence does contain cartilage, as in Case XXVI, the removal of the primary growth has been very incomplete, so as to leave portions of the original cartilage *in situ*.

In only one of the cases examined by the writer has there been metastatic invasions of the lymph nodes. This case (IV), however, was complicated by what is probably to be classed as an epithelial tumor arising in a mixed growth of the parotid. Both the remains of the mixed tumor structure and the epithelial alveoli are to be found side by side in the same section. None of the other cases of the mixed type of tumor furnished metastases involving the regional lymph nodes. Tanaka, however, considers the invasion of the regional nodes as a very frequent occurrence with the endothelial tumors, but his cases are to be viewed with considerable doubt, as none of them were from the salivary glands, and the histories and the pathological reports would incline one to regard the cases which he describes as sarcomata, especially those arising in the skin. The case of Griffini and Trombetta may be an exception to the rule of the non-invasion of the lymph nodes. The tumor was cartilaginous and of sixteen years' duration. At the close of that time it began to grow rapidly, and on the death of the patient was found to involve the lung, the pleura, the cervical, and the bronchial lymph nodes. In the tumor masses in the pleura and the lung some cartilage was detected, but none in the lymph nodes. The tumor had invaded the bone marrow and the vessels of the neck, and sent long strands down along the channels of the neck, so that it is possible that the metastases were by direct extension from the primary growth. The authors class it as a chondrocarcinoma of the submaxillary gland, so that it may fall under the same class as Case IV, the drawing appended to the paper showing a growth of carcinomatous type.

The metastases of the mixed tumors are of two varieties, local and remote. In the first form the recurrence is usually of the same type as the original tumor; that is, the general morphology of the original growth is retained and the recurrence may contain cartilage, mucus, and hyaline tissues. When the recurrences extend over a long period the tumor may gradually lose its characteristic morphology and resemble a sarcoma very closely (Case XXV). This change should be carefully distinguished from that in which the tumor stroma undergoes a sarcomatous change with the production of a typical sarcoma with rapidly growing and wide-spread metastases. In the secondary growths of this type the stroma retains no trace of the embryonic structures, no cartilage or hyaline tissue is present, and the tumor cells do not show their original alveolar arrangement. Cases XLI and XLII are examples of such changes. In a case reported by Barozzi and Lesné, in which a recurrent tumor occupied the entire left side of the face and neck, the cervical and tracheal lymph nodes were invaded by the new growth. The original tumor appears to have been not a cylindroma, as it is designated by the writers, but an epithelioma with mucous degeneration of the connective-tissue stroma. In fact, the term cylindroma as used by the French writers has not the same significance as when used by Sattler and other German writers, but in general may be considered as designating an epithelial tumor with degeneration of the stroma.

Occasionally the growth invades the wall of one of the large veins of the neck, and emboli are carried in this way throughout the body, as occurred in Case XLI of my series; but this is rare, and the growth, as a rule, remains fairly well localized, local recurrences being not infrequent unless the removal of the original growth has been very thorough, a condition often difficult of realization in the parotid growths owing to the close contact of many of the growths with the facial nerve. Case XXV is an excellent example of repeated recurrences extending over a long period of time, while Case X is an example of a prompt recurrence with a final radical removal of the growth. Cases XXVII and XXXVI are examples of frequent recurrences with the final death of the patient.

Billroth reports a case in which, during the course of twenty-three years, nine operations were performed to remove local recurrences.

The cases of primary endotheliomata of the cervical lymph nodes which exist in the literature (Zahn, Hoffmann, and Volkmann) ran an exceedingly malignant course, while the single case which the writer has had opportunity to observe was quite benign and did not recur after removal (Case XIX).

RÉSUMÉ OF THE MORPHOLOGY OF THE TUMORS.

The details of the microscopic description of the mixed tumors are best subdivided into two groups,—one embodying the structure of the stroma; the other, the structure of the parenchyma.

The connective tissue of the tumors is very variable in structure and amount. In the denser forms, especially in the tumors from the pharynx and in some of the parotid tumors, the connective tissue is arranged in very firm, dense bands traversing the growth, and also surrounding it, in the form of a firm fibrous capsule. The bands traversing the substance of the tumor divide it into a series of trabeculæ in which the cellular structures lie. These bands, as well as the capsule, stain intensely with the Van Gieson stain, and also take a very clear and sharp stain with the Mallory phosphotungstic acid hæmatoxylin, especially if, as Ribbert recommends, the material has been fixed in Zenker's fluid. There is only occasionally evidence of a basement membrane of connective tissue about the alveoli of the parenchyma cells such as exists in the normal parotid or submaxillary. The finer fibrillæ cannot be demonstrated between the cells of the alveoli nor between the cells of the solid strands of the so-called endothelial cells, even when the tissues are stained deeply with the phosphotungstic mixture or Van Gieson's stain.

The absence of connective-tissue fibrillæ between the cells of a tumor is usually regarded as indicating the epithelial origin of the tumor cells, since they are usually present between the cells in sarcomata. Some writers, notably Barth, claim to have been able to demonstrate the presence of fine fibrillæ of connective tissue between the cells of the so-called endothelial masses by means of special stains. Barth recommends Rosin's stain, which is a modified Ehrlich-Biondi tissue stain.

The staining solution is made by taking four centigrammes of the dry Ehrlich-Biondi mixture, dissolving it in 100 cubic centimetres of water, and adding to the solution seven cubic centimetres of a half per cent. aqueous solution of acid fuchsin. Paraffin sections remain in this for five minutes and are then washed for two minutes in water, differentiated for ten seconds in 1 to 2000 acetic acid, dehydrated in alcohol, cleared in xylol, and mounted in dammar. The nuclei are green, the connective tissues are red.

Barth's drawings are excellent, but not absolutely conclusive; and it seems possible that he has stained some of the spindle-shaped connective-tissue cells which often lie between the flat endothelial cells, and that true fibrillæ are not demonstrated. The writer has tried this method on a number of tumors of different types, and has not been able to demonstrate this condition; nor has it been possible to do so with the phosphotungstic acid method, though the fibrillæ can be easily shown with this stain between the cells of many of the sarcomata which have been used as a control for the method.

In the softer tumors the connective tissue is correspondingly looser in texture; it is often œdematous, and very frequently is replaced by myxomatous tissue. The myxomatous changes are frequently seen, but do not seem always to be due to a degenerative process, as was considered probable by Volkmann, but rather to an actual presence in the tumor of embryonic tissue of the myxomatous type. The evidences for this assumption lie in the nature of the tissue, which does not resemble the ordinary myxomatous degeneration in connective tissue, but is more like the tissue of the embryo with its long branching cells. The quite constant association of the myxomatous tissue with cartilage is another reason for assuming its origin to be embryonic, for, as will be seen later, there are many reasons for supposing that the cartilage is derived from the Meckel's or Reichert's cartilage of the developing embryo.

Embryonic connective tissue without myxomatous structure is frequently found in these tumors. It consists of a loose fibrous tissue stroma with spindle cells scattered through it in small numbers. The spindle cells form a portion of the fibrous net-work of the connective tissue by giving off from their cytoplasm long fibres which, in properly stained specimens, can easily be traced for a considerable distance.

The cells of the stroma have been described more or less while discussing the structure of the connective-tissue elements, so that only a review is necessary here. These cells vary in number and morphology in the different tumors, depending largely upon the condition of maturity of the connective tissues present. The stroma of the dense growths contain but few cells, and these are of the familiar connective-tissue type; that is, of long spindle-shaped cells with small, evenly staining nuclei without definite chromatin net-work, and rarely showing mitotic figures. The tumors in which connective tissue of a more embryonic type is present, and the tumors of the previous group in which portions of the stroma have undergone a sarcomatous change, show cells with large nuclei and well-marked chromatin net-work. The cell body is more prominent and more sharply outlined and mitotic figures are occasionally seen. In the myxomatous and cartilaginous portions the cells are either the branching cells regularly seen in myxomatous tissue or they are the encapsulated cells of hyaline cartilage with their double nuclei. In the tumors examined by the writer no evidences of proliferation were found in either the cells of the myxomatous tissue or in those of the cartilage, though such appearances in the cartilage of these tumors have been noted by von Ohlen.

The large flat cells of the tumor parenchyma are also found scattered through the myxomatous portions of the new growth and about the periphery of the cartilage, which fact has given rise to speculations concerning the origin of the cartilage from the flat so-called endothelial cells, or of the flat cells from the cartilage. These flat cells may be few in number and diffusely scattered throughout the stroma, or they may be collected into strands spreading out diffusely through the myxomatous or fibrous tissue and also entering into close relationship with the cartilaginous areas. Some of these cells in the myxomatous portions may be observed to be closely connected with the stroma by giving off the fibrillæ into its substance, others retain the oval or polyhedral form of the flat epithelial cells lining the alveoli.

Giant cells are not uncommon, especially on the cellular borders of the myxomatous areas into which they often project. The mechanical conditions here which permit the free growth of the cells into the soft myxomatous areas may possibly account for the condition, especially as similar pictures have been seen in pleural growths where the same freedom of growth is possible.

Cartilage is found in about one-fourth of the mixed tumors of the salivary glands and of the facial region which the writer has been able to examine; other observers have found it in half the tumors examined. Osteoid tissue is fairly frequent, while bone is rare. Bone was present in no one of the tumors examined by the writer.

The cartilage is either hyaline or fibro-elastic. As a rule, there are numerous fine elastic tissue fibrillæ scattered through even the more typical hyaline cartilage in the form of a fine mesh-work easily demonstrable by Weigert's method for elastic fibres.

The cells of the cartilage are usually similar to those of hyaline cartilage under normal conditions; they may be encapsulated or free in the homogeneous stroma. Occasionally, however, there are variations in the arrangement and the number of the cartilage cells and tumor cells which render it easy to distinguish from the normal tissue. The most frequent anomaly is the presence of a large number of cells without the capsule which usually surrounds them. A number of cells may collect in small masses in the substance of the cartilage and calcification may take place, the salt deposited being most frequently the sulphate of calcium. Finally, the substance of the cartilage may soften and produce small cysts containing a clear brownish fluid. The cartilage may form a greater part of the tumor, or it may be very scanty in amount and merely scattered through the tumor in small islets. In all cases it is in very intimate connection with the connective-tissue stroma and cells, and also with the so-called endothelial cells of the tumor.

The *elastic tissue* content of these tumors is not mentioned in detail in any of the monographs on the subject. Indeed, the literature on elastic tissue in tumors is still meagre and contradictory in its statements. Melnikow-Raswedenkow found no newly formed elastic fibres in tumors, all those present were derived from the organs in which the growths occurred. He examined connective-tissue tumors, epithelial tumors, teratoid tumors and cysts, and concludes that there is but little elastic tissue in any one of these growths, and also that the elastic tissue of the organs invaded is only mechanically influenced by the tumor cells in their growth.

Williams, on the other hand, found that a few fine fibres are occasionally seen in the newly formed stroma of the carcinomata, but only in tumors in which the stroma was especially abundant.

Alice Hamilton describes a fibrosarcoma of the brain in which numerous elastic fibres could be demonstrated which she considered as newly formed, inasmuch as they were not confined to the region of the blood-vessels, which is the only site of elastic fibres in the brain substance. Huguenin, in an adenoma (?) of the testicle containing cartilage, glands, and epithelial masses, says that the cartilage in his preparations contained no elastic fibres, but admits that the stain was not entirely satisfactory, owing to the method of preserving the material. In some of my own specimens of mixed tumors of the testicle elastic tissue was very abundant throughout. Gliuski found little or no elastic tissue in a mixed growth from the œsophagus. K. Landsteiner is the only observer who mentions the abundance of the elastic fibres in the salivary tumors.

The elastic tissue in the mixed tumors is very much more abundant than in the sarcomata or carcinomata. In the latter it is largely confined to the pre-existent stroma, and there is only a moderate new production, and this in the region of the vascular system. In the mixed tumors, however, the stroma of the growth is penetrated by a fine mesh-work of fine and coarse fibres of elastic tissue. These are specially abundant in the dense fibrous tissue of the capsule and the trabeculæ of the more fibrous growths. In the soft embryonic fibrous tissue of the more cellular tumors the elastic tissue is in the form of very fine branching fibrillæ having no connection with the blood-vessels. In the cartilaginous parts the elastic tissue penetrates all portions as a fine net-work, not so dense, however, as in true fibro-elastic cartilage. The elastic fibres usually encircle the alveoli in considerable numbers, but do not penetrate between the cells lining the alveoli. When the stroma cells diffuse out through the connective tissue, or even when they remain in solid strands, the finer elastic fibres often penetrate between the cells. The fibre net-work may surround a single cell or it may surround a group of several cells.

Blood-vessels are infrequent in these tumors, and when present seem to bear little or no relation to the cells of the parenchyma. They are usually seen in the connective-tissue trabeculæ of the more fibrous growths and present no peculiarities.

Small areas of fat tissue are to be found in a number of the mixed tumors inside the capsule of the growth and lying in the connective-tissue stroma. They are quite independent of the fat of the surrounding connective tissue, the gland with which the tumor is in relation, and are probably derived from the embryonic connective tissue which forms the stroma of the growth.

The same is probably true of small lymphoid areas which are not uncommon in the mixed tumors. Their derivation is in all probability the lymphoid tissue of the buccal and pharyngeal mucosa, and is especially well marked in the cysts and clefts from the branchial pouches which have persisted until adult life, and still retain a well-developed envelop of lymphoid tissue about the epithelium lining the cavity of the cyst or sinus.

The Cells of the Parenchyma.—The cells of the parenchyma of the mixed tumors are arranged either in alveoli or in solid strands, which are often connected with alveoli at some portion of their extent. When arranged in alveoli they are large and flat, resembling epithelial cells in their general grouping, but differing from ordinary epithelium in having an oval homogeneous nucleus without a well-marked nuclear net-work, the entire nucleus staining diffusely. The cells under ordinary conditions do not show intercellular bridges nor spines, such as are frequently seen in epithelial cells. These cells may be high and cylindrical; they may be cuboidal or polygonal; and, finally, if the lumen of the alveolus be filled with accumulated material, they may be flattened out into low cells resembling the endothelium lining the blood-vessels. In a number of the tumors examined, instead of alveoli being present the parenchymal cells are in long strands, as above indicated, extending through the tissues closely attached to the connective tissue of the tumor and often containing long spindle-shaped cells of an evidently connective-tissue nature. The cells of the strands may also give off long fibrillar prolongations to the connective tissue. This can be best seen in the myxomatous portions of the tumor, for there the fibrillæ can be more easily traced.

As was stated under the heading of the fibrous stroma, no connective tissue can be made out between the parenchyma cells, either when they are in alveoli or in strands. When sections are stained either with Van Gieson or with Mallory's connective-tissue stain, fibrillæ can occasionally be demonstrated between the cells, but this appearance is due to the spindle cells lying between the others, and is not of constant occurrence. A basement membrane is not usually present about the alveoli, but the elastic fibres are occasionally very abundant around them.

In a few tumors the cells lining the original alveoli are crowded together by connective-tissue growth and degeneration, so that the lumen is lost and the whole structure distorted in much the same way as in an intracanalicular fibroma of the breast. Case LIX is an excellent example of this form of distortion. (Plate VIII, Fig. 2.)

An important point of difference between the cells lining the alveoli of this form of tumor and the cells of an epithelial new growth is that the normal endothelium lining the lymph spaces can generally be seen under a layer of epithelial cells, while it cannot be so seen in the alveoli of the mixed tumor cells. That this is not always true can be seen in Case XX, where the so-called endothelial cells of the tumor can be made out advancing over the normal endothelium lining a lymph space, just as the cells from a carcinoma may be seen to advance over the endothelial cells of the lining of the lymph channels of a lymph node. (Plate II, Fig. 2.)

As previously stated, Volkmann claims that the so-called endothelial cells lining the alveoli do not shrink away from the connective tissue with which they are in contact, as is the case in carcinomata, even when the tissue is considerably shrunken by fixing agents. Borst and others have shown, however, that this distinction cannot be strictly held, for in some of the endothelial tumors the cells do shrink away from the connective-tissue walls of the alveloli, and in carcinomata it is easy to find areas where the epithelial cells remain in contact, even though there is considerable shrinkage during the hardening process. It is true, however, that the separation occurs more frequently in the carcinomata and is rare in the mixed tumors.

Epithelial cells with well-marked spines are more or less abundant in the parenchyma of eight cases in my series of fifty-nine. They are arranged very frequently in pearls, the centre of the pearl staining strongly with eosin, as in the pearls from the ordinary epitheliomata of the skin. When stained with Kromayer's modification of Weigert's fibrin method, well-marked keratohyaline granules can be made out in some of the cells at the periphery of the pearls, and also a moderately well-marked fibrillation which passes from one cell to the other. (Plate V, Fig. 2.) The intercellular bridges are well marked in many of the pearls and in some of the alveoli in which no pearl formation has taken place.

In six of the other tumors examined, which did not contain pearls, cell alveoli were found which bore a very close resemblance to the ducts of an atrophic salivary gland. These alveoli were lined with a single layer of cuboidal cells and possessed a well-marked basement membrane. (Plate I, Fig. 2.)

Three of the smaller tumors were embedded in paraffin and sectioned in a complete series. In no one of them were well-marked epithelial spine cells demonstrated. A large number of sections from the other tumors were examined, but no spine cells were found; so the presence of epithelial spine cells cannot be regarded as a constant or even a frequent occurrence, as Hinsberg is inclined to believe.

Connected with the pearls, branching strands of cells are often seen, which lack the characteristic morphology of epithelial cells and resemble the strands considered by Volkmann as endothelial in nature.

DISCUSSION OF RESULTS.

If we look over the case histories of a series of tumors of the type which we have described, in order to obtain some clue to the conditions which surround their origin, we are struck, in the first place, with the fact that all these new growths arise in regions of the body which are characterized by two conditions,—one, the presence of complex organs either of epithelial or mesoblastic origin, and, secondly, from an embryological point of view, by an extremely complicated course of development.

Both of these conditions obtain in the facial region and in the region of the development of the kidney, ovary, and testicle, to which areas these complex tumors are practically confined, if we except the site of the postanal gut, where complex forms also occur under precisely the same conditions.

If we consider these tumors as a whole, we must notice that they contain elements which are derived from the mesoblast at a comparatively early stage of differentiation. Evidently, cells of mesoblastic origin must have been left in these situations at a period when they contained all these tissue possibilities and before a final differentiation took place, for the change into a definitive form of cell precludes the possibility of further differentiation; as, for example, the final changes of undifferentiated embryonic mesoblast into the highly specialized cell forms, such as muscle or cartilage, preclude further changes except of a regressive type.

It is interesting to observe more closely the association of these tumors and malformations which result from imperfect adjustment of the tissues which go to form the facial region. These malformations are the dermoids of the orbit and the eye, the cysts and fistulæ which arise from the imperfect closure of the thyroglossal duct or the branchial clefts, the imperfections from lack of union of the lateral processes forming the mouth and cheeks, and, finally, the malformations of the ear, with either an accessory tragus or mandibular or cervical tubercle. In Case L, a small congenital parotid tumor was present in the upper part of the parotid, while just behind it was a supernumerary spur of cartilage derived from the non-union of the spina helicis with the helix. There was present also an auricular fistula in the helix resulting from the same lack of union between the helix and the spina. (See Schwalbe and Gradenigo.) The tumor was a complicated growth, containing among other things a considerable amount of hyaline cartilage; the spur, on the other hand, contained yellow elastic cartilage, and was therefore not, in all probability, derived from the same source as that in the tumor; but the connection of the tumor of the parotid with the other congenital lesions is strongly suggestive of the simultaneous displacement of both sets of remnants.

The derivation of the cartilage which these complex tumors contain has always interested pathologists. There are two chief possibilities to be considered; one, which has long been held, is that the cartilage is derived by a process of metaplasia from the connective tissue of the tumor or from the tumor cells; the other is that the cartilage is either a remnant left in the formation of the branchial arches, or that certain cells are left from that portion of the embryo which is to finally form these arches, and that these cells are capable of developing into either an undifferentiated fibrous or mucous tissue or into the more highly differentiated form of cartilaginous tissue.

Virchow's idea was that the cartilage originated in the connective tissue, much as cartilage arises from the periosteum of bone, and this view is developed in Volkmann's paper. The latter holds that the process is "exceedingly simple," and consists in a chemical alteration of the intercellular substance by which the fibrillæ of the connective tissue are softened and dissolved into a more or less homogeneous mass of basement substance, and thus forms either cartilage or myxomatous tissue. The flat cells of the tissues then undergo a metamorphosis in response to that which has taken place in the connective tissue, and become either encapsulated cartilage cells or emit fibrillæ and become the branching cells of the myxomatous tissues. All transitions can be observed between the cells and the connective tissue; but the most frequent process is the transformation into myxomatous tissue first, and then an alteration of the cells and the stroma into cartilage. Volkmann and von Ohlen find that the cartilaginous portions are often the site of very active proliferation, and that they form long strands of cells similar to those seen in other parts of the growth. Against all these views are the facts that the cartilaginous tumors are of extremely slow growth clinically; that mitotic figures have not been found in the cells of the cartilage by the writer and many other observers; that the elastic tissue is not arranged in the cartilaginous portions as it would be if the pre-existing connective tissue had merely become softened, but is in fine fibrils scattered throughout; that the cartilage is not found in the metastases, but only in local recurrences; and, finally, that these degenerative changes in connective tissue with the formation of cartilage do not take place in other tumors which contain abundant connective tissue, but only appear in a certain narrow group of tumors which are in all probability congenital in their origin.

Cohnheim, in his lectures on general pathology, said long ago that "the germs of the cartilaginous tumors of the parotid region are unused remnants of the cartilaginous portions of the branchial arches."

Klebs believes that when the organism has reached a certain physiological point of development and the cells possess a degree of specific stability, that cartilage can only be produced from embryonic remnants.

Orth also holds the same view of the origin of the cartilage, while most of the special writers on the subject support Volkmann in deriving the cartilage from the connective tissue.

In general, it may be said that the idea of the change of one tissue into a closely related form is gradually losing the general acceptance which it once possessed, and such changes are more and more being considered as due to embryonic errors of development.

Ribbert, in his latest publication, when speaking of the metaplasia of connective tissue into cartilage or myxomatous tissue, says that such changes even within these narrow limits are very infrequent in their occurrence, and that there is considerable reason to suppose that these appearances may be due to embryonal misplacements of tissues. In another section he considers it probable that most, if not all, of the pure myxomata are due to some congenital remnant of mesoblast displaced at a stage when it contained the possibilities of myxomatous development. Lubarsch states that while it is undoubted that the "epithelia" lining the serous cavities and the blood-vessels can produce connective tissue, which can best be seen in the organization of thrombi and the inflammation and foreign body irritation of the serous cavities, the question of the metaplasia of endothelial cells into cartilage cells is more than doubtful. Benecke considers that this change is possible in tumors, but the condition may be due to an embryonic misplacement of cells. Certainly the fact cannot be regarded as proven. The possibility of the metaplasia of true ento- or ectodermal cells into connective tissue has never been positively shown. Kromayer's interpretation of the pictures which he obtained in the examination of the soft nævi of the skin has never been widely accepted, and the view of Unna that the nævus cells are epithelial in origin is now generally received. It is especially difficult to prove the metaplasia of epithelium into connective tissue in the skin because the epithelial cells become flattened and drawn out into long spindle-shaped forms which often lie in close connection with the connective-tissue fibrillæ of the pre-existing stroma, so that this apparent change into connective-tissue cells is to be regarded as the result of mechanical action, and true connective-tissue cells in the biological sense have not been produced. This mechanical change may also occur in the epithelial masses of the salivary mixed tumors.

The main weight of the evidence seems to be on the side of the congenital misplacement of cells which have the power to form either cartilage or myxomatous tissue. The same explanation would account most simply for the presence of fat and lymphoid tissue in these tumors. Fat tissue is not ordinarily seen in tumors as a portion of the growth itself, but usually as a part of the tissue through which the tumor may be growing. But in many of the congenital tumors,—for example, those from the kidney,—whose origin from embryonic misplacements is more definitely settled than in the case of these complex tumors of the parotid, the presence of fat tissue and striated muscle in intimate relationship is regarded as a valuable evidence of the derivation of the tumor stroma from the mesoblast at a time when the kidney rudiments were in close contact with the muscle-plates of the middle layer of the embryo.

The examination of sections of human embryos of from six to twelve weeks of age shows that such embryonic displacements may easily occur in the region of the salivary glands. In transverse sections through the head of embryos of this age, the parotid and the submaxillary may be seen as small outgrowths from the floor of the mouth, lying almost in contact with the first and second branchial arches, or rather with the cartilage which these arches contain. Very often tubules of the gland may be found to be surrounded by the cells of the perichondrium.

Inasmuch as the arches reach their development at or about the fourth week, and at that time contain the cartilaginous tissue which forms Meckel's and Reichert's cartilages, while the parotid does not appear until the sixth or eighth week, for any embryonic remnant to contain both parotid and cartilage, the tissue must have been displaced before the fourth week. It is not therefore a portion of parotid tissue which is displaced, but a portion of the epiblast which is to line the buccal cavity, together with some of the underlying mesoblast, the latter carrying with it the whole group of mesoblastic possibilities,—cartilage, myxomatous tissue, fat, and even muscle.[1] This necessarily early displacement of the tissues would make up the tumor accounts for the great variability of the mesoblastic and epiblastic structures present in the growth and the close intermingling of cartilage, myxomatous tissue, hyaline, fat, muscle, and bone, together with cells of both epithelial and connective-tissue types.

This early derivation of the remnants is also a point upon which Wilms has rightly insisted as rendering superfluous the explanation which Hinsberg finds necessary to make in order to account for the presence of cornified epithelium in the midst of these complex tumors. Hinsberg has to assume a metaplasia of the parotid glandular epithelium into epidermal cells; but if it be remembered that the displacement takes place before the buccal epithelium has become differentiated into parotid, and while it still retains the qualities inherent in that epithelium, that is, of forming epithelial cells for the lining of the buccal cavity, the assumption of metaplasia to account for the presence of the epidermal cells is quite unnecessary.

Hinsberg's further assumption that the epithelium might possibly be derived from the rudiments of the tympanum, which at this stage lies quite close to the parotid, is rendered doubtful by the fact that epithelium has been found in the submaxillary tumors, but the distance of the submaxillary gland from the tympanum is so great at all stages of development that such a displacement of tympanic epithelium is quite out of the question.

If now we turn from the elements of the stroma to the parenchyma of these tumors, the most striking feature is the presence of numerous cellular structures arranged either in solid strands or in the form of alveoli lined with flattened cells. Some of these cells are evidently epithelial in origin from their morphology, which is that of spine cells with well-developed intercellular bridges and keratohyaline granules or of tubules lined with cylindrical epithelium. The latter forms occur, so far as the tumors examined show, but rarely in any of the new growths from the facial region; they are frequent, however, in the tumors of the testicle. The other type of cells is that which has long been designated endothelial, because these cells possess a morphological aspect strikingly similar to the endothelia lining the lymph spaces.

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[1] See report of a rhabdomyoma of the parotid by Prudden, American Journal of the Medical Sciences, 1883, page 438.

Three views are possible as to the origin of the cells. One, that they are endothelial in nature and derived from the endothelium of the lymph spaces; second, that they are epithelial and derived either from a misplaced portion of the parotid or from a misplacement of the mesoblast and epiblast at a period when the cells have not as yet developed into the highly differentiated gland cells, but contain the possibilities of such development only, as is explained above in the discussion of the probable origin of the cartilage; third, that the tumors contain both endothelial and epithelial elements.

We will first take up the endothelial view as presented by Volkmann and his successors.

1. Is the endothelium capable of producing tumors? That this is probable is shown by the cases of tumors occurring in lymph nodes where epithelium cannot be present, and also in tumors of the bone marrow and the spleen, such as have been recently collected by Bovaird. The splenic tumors are, however, more probably hyperplastic growths than true tumor formations. The tumor reported by Sailer must also be regarded as a growth from the endothelium of the vein in which it was found. The tumors of the dura are no doubt of an endothelial character.

2. Are the parenchyma cells of the complex salivary tumors derived from the endothelium? The various facts which have been adduced to substantiate this view are:

(*a*) The cells resemble endothelial cells from a purely morphological aspect. That this is of slight value in the determination is shown by Case VI of my own series, in which typical epithelial cells can be found in strands of cells otherwise conforming in all morphological points to endothelium. The same is true of cases reported by Hinsberg, Landsteiner, and Wilms in which spine cells have been found.

(*b*) The cells of the tumor are continuous with the cells of the peripheral lymph spaces in the capsule of the tumor, and that the endothelium of these spaces takes part in the growth of the tumor. Ribbert, Borst, and others have shown, however, that the lymph-space endothelium does not take part in the tumor growth, and that the spreading of cells of a new growth along lymph spaces, either with or without active growth of the lymph-space endothelium, is possible in carcinoma as well as in the so-called endothelial tumors. Ribbert has also called attention to the fact that the spaces which Volkmann regarded as normal lymph spaces in the fibrous tissue were not in fact lymph spaces, but tumor alveoli.. The apparent new growth of endothelium in the spaces is due to the fact that the cells of the tumor grow over the endothelial cells already present and give the appearance of an hyperplasia of the pre-existing cells.

(*c*) The argument based upon the supposition that the cells of the endothelial tumors do not shrink away from the walls of the lymph spaces, and that the original endothelial cells cannot be seen under them, has been shown, by the observations of Borst, Lubarsch, and many others, to be incorrect. One of my own cases shows this shrinkage in many parts of the tumor. (Case XX, Plate II, Fig. 2.)

(*d*) Ribbert, Lubarsch, and others have shown that the fact upon which so much stress has been laid, that the solid strands of cells are in intimate connection with cells of undoubted mesoblastic origin, has but slight value in deciding that the two groups of cells are of identical origin, for such secondary unions of true epithelial and connective tissues are not infrequently observed in the epithelial tumors of the skin.

(*e*) The fact that the tumors are not closely connected with the salivary glands, and that the cells of the new growth are not connected with those of the gland, but are separated from it by a capsule, does not prove that the cells of the tumor are not of epithelial origin, but only that they were separated from the glandular rudiments before the latter were enclosed in the capsule normally surrounding the gland. The formation of this capsule takes place about the fourth month of fœtal life, while up to this time the acini of the gland are in close relationship with the periosteum of the inferior maxilla.

If we take up, on the other hand, the considerations which point to the view that the cells of these complex tumors are derived from the outer layer of the embryo, we find that they are based upon the following facts:

(*a*) Epithelial cells with intercellular bridges and keratohyaline granules are found in a few of these tumors, which are otherwise of a typical endothelial morphology. The epithelial cells lie in masses which would under ordinary circumstances be considered as very closely related to the surrounding connective tissues.

(*b*) Well-formed tubular glands with a basement membrane and a lumen filled with a homogeneous secretion are found in a few of these tumors, which are otherwise typically endothelial according to Volkmann.

(*c*) A great proportion of these tumors contain alveoli filled with a material resembling the colloid secretion of the thyroid or the material which may be found in the alveoli of an atrophic salivary gland.

(*d*) There is no connective tissue between the cells, as is generally the case in tumors of a mesoblastic origin. This is seen in stained preparations and in sections which have been either shaken out or pencilled to remove the cells of the parenchyma.

(*e*) These tumors occur only in or near epithelial structures and in regions in which congenital inclusions in the form of dermoids and cartilaginous remnants are fairly frequent. The intimate mixture of tissues of widely different type in a single tumor is a strong presumptive evidence that the growth is of congenital nature.

It is difficult to apply a suitable name to this group of tumors, and yet it is advisable to do so, if for no other reason than to call attention to the fact that they cannot be classed as adenomata, nor as epitheliomata or carcinomata, nor yet as sarcomata. From each of these groups of tumors the complicated growths which we have studied are separated by their morphology alone. The writer prefers to return to the old name of "mixed tumors," or, perhaps better, complex tumors, though the introduction of the latter might be justly criticised as adding a new name to our already complicated nomenclature.

The problem of the exact nature of these growths cannot be definitely settled so long as we must rest our distinctions upon morphological or histogenetic differences. The experiments which Ribbert, Lubarsch, and many others have carried out on the results of the transplantation of normal glandular tissues have given us only studies upon the atrophy and partial regeneration of fragments as grafted upon other tissues and under the most unfavorable conditions for permanent growth. We cannot expect too much of the transplantation of mature, highly differentiated tissues into an unfavorable environment, nor have the results of the transplantation of embryos or fragments of embryos afforded the results for which we hoped. The change of place and environment must be made at an earlier date and in a manner somewhat less crude than has been practised heretofore. Experimental teratology has at present only given results when applied to the lower forms of animal life.

CONCLUSIONS.

To sum up the results of this study in a few words:

I. There is a group of extremely complicated tumors occurring in the facial region which contain elements from both epi- and mesoblast in most intimate relation to each other.

II. The complicated structure of the stroma, containing as it does elements such as embryonic connective tissue, cartilage, bone, fat, and lymphoid tissue, and very rarely striated muscle, is explained most easily by the assumption of an embryonic misplacement of mesoblast.

III. The structure of the parenchyma is so slightly characteristic in morphology that its epithelial nature in all cases can only be considered as probable; yet in about 24 per cent. of the tumors examined the presence of epithelium is undoubted. The form and relationships of the cells of the parenchyma do not furnish sufficient data to justify these cells being regarded as of endothelial origin.

IV. The theory of early embryonic displacement of epiblastic tissue during the process of formation of the parotid and submaxillary glands and the branchial arches may account for many of the morphological peculiarities of the cells of these tumors, especially the lack of many typical features which we associate with epithelium. The same condition may be seen in the epithelial cells of the congenital moles, in which the epithelium is with difficulty distinguished from connective-tissue cells, owing to its close connection with the stroma of the tumors and its undifferentiated type.

V. The mixed tumors of the salivary glands run a clinical course strikingly different from the sarcomata and carcinomata in that they are slow growing and generally benign. The regional lymph nodes are not invaded, and recurrences are likely to remain local in a considerable proportion of the cases.

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